The role of thorax-ct in mediastinal staging of the nonsmall cell lung cancer, revive our memories

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Abstract

Aim: In this study, the role of thorax-CT was examined in evaluating intrathoracic lymph node in patients diagnosed with preoperative Non-Small Cell Lung Cancer (NSCLC). This study aims to review our existing knowledge on thorax-CT, which is the first examination method used in the evaluation of lung masses and to discuss its performance in mediastinal staging based on data of patients in Turkey. Material and Method: 510 cases selected by the criteria identified between January 2009 and July 2011 were included in the study. Lymph nodes, their sizes in thorax-CT, histological type of the tumor, removed mediastinal lymph nodes and pathology results were examined. Results: As a result of the statistical analyses, the sensitivity of thorax-CT in detecting metastatic intra-thoracic lymph nodes was calculated as 75.7%, specificity 41%, negative predictive value (NPV) 85% and accuracy 48.4%. NPV and positive predictive value (PPV) were also calculated for N1 and N2 diseases. False positive rate of thorax-CT in detecting N1 disease was calculated as 53.6%, and the false negative rate was calculated as 28.7%. The false positive rate in detecting N2 disease was 64.6%, and the false negative rate was 20%. Discussion: While thorax-CT is essential in mediastinal staging in NSCLC, we believe that thorax-CT alone is not sufficient and needs to be supplemented with other scans and invasive methods. Due to the increased health costs, the waste of time and labor due to the use of more than one scan, Positron Emission Tomography and CT should be used more frequently in especially in lung cancer.

Keywords

Non-Small Cell Lung Cancer; Lymph Node; Mediastinal Staging; Tomography

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Introduction

Lung cancer, with increasing incidence and mortality rates, is one of the most important health problems in the World and almost one-third of deaths from cancer are due to lung cancer. Only 15% of the patients can survive for 5 or more years after being diagnosed [1].

In non-small cell lung cancer (NSCLC), when diagnosed 50% of the patients have mediastinal lymph node involvement and less than 33% are suitable for surgical resection [2,3]. To increase the success rate of surgical treatment, early diagnosis is crucial. For accurate staging of NSCLC, location, and size of the primary tumor (T factor), regional lymph nodes (N factor) and distant metastasis (M factor) need to be identified. For this, methods such as Thorax CT, Magnetic resonance imaging (MRI), Scintigraphy, Ultrasonography, Positron Emission Tomography (PET) are used [4].

In patients without distant metastasis, mediastinal lymph node involvement is the most important factor in determining treatment and prognosis. Therefore, accurate evaluation of mediastinal lymphatic metastasis is crucial in preoperative stage [5]. Thorax-CT, which is used as the initial method for identification of metastatic mediastinal lymph node, has limited sensitivity and specificity in showing metastasis in enlarged lymph nodes [6]. On the other hand, mediastinoscopy which is the 'gold standard' with excellent sensitivity and specificity rates in mediastinal lymphatic staging has the disadvantage of being invasive. The aim of this study is to determine sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy rates of thorax-CT in detection of metastatic intrathoracic lymph nodes in patients with NSCLC, to assess the need for invasive methods through additional scanning methods and to refresh our knowledge, by comparing thorax-CT findings for intrathoracic lymph nodes and histopathological results obtained through invasive methods.

Material and Method

Cases who were diagnosed with NSCLC and who underwent thorax-CT and PET-CT, and surgery for treatment and/or staging between January 2009 and July 2011 were retrospectively reviewed. The study included all surgical cases who underwent histopathological examination apart from fine needle aspiration biopsy. 28 cases out of 538, who underwent chemoradiotherapy were excluded from the study.

Preoperative assessment of all cases included anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemistry and hemogram tests, coagulation tests, postero-anterior and lateral lung graphics, thorax-CT and PET-CT. Tests and invasive procedures were performed based on TNM staging. Age, gender, preoperative diagnostic tests, location of the mass, enlarged intrathoracic lymph node on thorax-CT (>1cm), SUVmax values of masses and all intrathoracic lymph nodes in PET-CT, operations performed, lymph nodes which were sampled/excised in operation, size of the tumor lesion, histopathological examination results of sampled lymph nodes and tumor type of all cases were recorded in the database.

Statistical analysis of the data was conducted with SPSS for Windows 11.5. Continuous variables were summarized by mean and standard error or by median (smallest – largest), and categorical variables were summarized by frequency and percentage.

Pearson's Chi-Square test and Fisher's exact test were used for assessing the significance of thorax-CT results in detecting metastatic and non-metastatic lymph nodes according to the histopathological results.

Using Pearson's Chi Square or Fisher's Exact tests, thorax-CT results were compared for every lymph node station to assess whether they are determinate in differentiating metastatic and non-metastatic lymph nodes according to histopathological results. Sensitivity, specificity, positive and negative predictive values, and accuracy rates were calculated to assess the diagnostic indicators.

Logistic regression analysis was undertaken to assess the role of thorax-CT results in differentiating metastatic and non-metastatic lymph node groups. Odds ratio and 95% confidence intervals were calculated for both examination results. Spearman's correlation test was used to assess the presence of any significant correlation between continuous variables.

P values less than 0.05 were considered significant.

Results

The study included 510 cases diagnosed with NSCLC preoperatively, who underwent thorax-CT, PET-CT, and surgery for staging/treatment between January 2009 and July 2011. 459 of the cases (90%) were male, and 51 (10%) were female. Their ages ranged between 26 and 87 with a mean age of 59,2+9,0.

A diagnosis of NSCLC was made preoperatively for 263 cases (51,5%) by transthoracic fine-needle aspiration biopsy, for 245 cases (48,1%) by bronchoscopic biopsy and for 2 cases (0,4%) by video-assisted thoracoscopic biopsy.

83 cases (16,3%) were diagnosed with diabetes mellitus. Since the presence of DM did not have any significant correlation in the evaluation of PET-CT results, the patients underwent scan according to their pre-scan blood glucose levels. The mean blood glucose level was 103 mg/dl (80-150mgr/dl).

The cases who underwent neoadjuvant chemoradiotherapy were not included in the study.

Among 510 cases which underwent surgery for staging and/or treatment after diagnosed with NSCLC, lobectomy was performed for 285 cases (55,9%), pneumonectomy for 196 cases (20,8%), wedge resection for 6 cases (1,2%), exploration for 1 case (0,2%), sleeve resection of the left main bronchus for 1 case (0,2%) and mediastinoscopy for 111 cases (21,7%).

In the analysis of tumor localizations, right lung tumor lesion was detected in 286 cases (56%), and left lung tumor lesion was detected in 224 cases (44%). 132 of the right lung tumors (25,8%) were in the upper right lobe, and 22 of them (4,3%) were in the right middle lobe, and 61 (11,9%) were in the lower right lobe, and 71 (13,9%) were in the hilar region.

The size of the masses ranged between 0,4 and 20 cm with a mean size of 4 cm. SUVmax value of masses ranged between 0 and 42,8. Mean SUVmax value of the masses was calculated as 12,6.

According to the histopathological examination to assess the tumor lesions based on the cell types, the most common carcinoma was squamous carcinoma with 229 cases (44,9%), sec-

ond one was adenocarcinoma with 162 cases (31,8%) and 36 cases (7,1%) had adenosquamous carcinoma, 17 cases (3,3%) had large cell carcinoma and 12 cases (2,4%) had sarcomatoid carcinoma. A number of cases, which were not divided into a type, was 54 (10,6%). Such cases were mostly the ones diagnosed with preoperative NSCLC and which only underwent mediastinoscopy.

The size of intrathoracic lymph nodes in thorax-CT and histopathological examination results for lymph nodes sampled/excised in operation were evaluated separately for each intrathoracic lymph node station. Lymph nodes measuring more than 1 cm in the short axis diameter that showed enlargement in thorax-CT were evaluated as metastatic, while lymph nodes under 1cm in size were evaluated as benign. Following the comparison of the results for the lymph nodes that were verified histopathologically and lymph nodes that were classified as metastatic or benign based on the lymph node size in thorax-CT, sensitivity, specificity, PPV, NPV, and accuracy rates were calculated for all intrathoracic lymph node stations.

The role of thorax-CT in determining the situation of intrathoracic lymph nodes and mediastinal staging in NSCLC was assessed for every station one by one (Table 1). Also, a general statistical analysis was conducted for N1 and N2. N1 lymph node stations which were assessed as benign in thorax-CT and histopathologically examined are 159. 130 of these cases had benign N1 lymph nodes, and 29 of them had metastatic N1 lymph nodes. There were 222 cases assessed as metastatic in thorax-CT and examined. Pathological results showed that 150 of these cases had benign N1 lymph nodes and 72 of them had metastatic N1 lymph nodes. Statistical analysis of the results showed that sensitivity of thorax-CT in NSCLC was 71,3%, specificity 46,4%. PPV 32,4%, NPV 81,8% and accuracy 53% (p: 0,002) (Table 2).

Table 1. Diagnostic performance rates for the thorax-CT in detecting metastatic and non-metastatic lymph node stations based on pathological results

LN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
2	88,9	72,4	20,0	98,8	73,6	<0,001
3	-	100,0	-	100,0	100,0	-
4	71,1	54,8	19,0	92,7	56,9	<0,001
5	66,7	59,1	18,7	92,6	60,0	0,026
6	20,0	87,5	11,1	93,3	82,6	0,619
7	75,0	48,4	11,8	95,5	50,7	0,011
8	10,0	99,4	50,0	94,7	94,2	0,113
9	0,0	99,6	0,0	95,3	95,9	1,000
10	75,0	43,3	16,0	92,3	50,4	0,021
11	0,0	99,6	0,0	75,8	75,6	1,000

LN: Lymph Node PPV: Positive Predictive Value NPV: Negative Predictive Value

Table 2. Diagnostic performance rates for the thorax-CT in detecting metastatic and non-metastatic N1 and N2 lymph node groups based on pathological results

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
N1	71,3	46,4	32,4	81,8	53,0	0,002
N2	80,0	35,4	22,2	88,5	43,7	0,004

PPV: Positive Predictive Value NPV: Negative Predictive Value

According to the thorax-CT scans of N2 lymph node stations, N1 lymph node stations which were assessed as benign in thorax-CT and histopathologically examined are 165. According to the pathological results of these cases, lymph nodes were benign in 146 cases and metastatic in 19 of them. The number of cases, which had metastatic N2 lymph node station in thorax-CT and examined was 343. According to the pathological results, lymph nodes in 267 of these cases were benign and metastatic in 76 cases. Following the assessment of N2 lymph node stations; sensitivity of thorax-CT in identifying the situation of lymph nodes was calculated as 80%, specificity 35,4%, PPV 22,2%, NPV 88,5% and accuracy as 43,7% (p: 0,004) (Table 2).

Multiple variable logistic regression analysis was undertaken to assess the role of thorax-CT and PET-CT with a SUVmax value of 2.5 for each lymph node station in differentiating metastatic and non-metastatic lymph node groups according to histopathological examination results. Odds ratio and 95% confidence intervals were calculated for both examination results. It was found that PET-CT had more statistically significant results (p<0.001) (Table 3).

Table 3. Diagnostic Performance of the Thorax-CT and PET-CT (SUVmax 2,5) in detecting metastatic and non-metastatic N1 and N2 lymph node groups accroding to the pathological results

Lymph Node	Thorax-CT			PET-CT		
	OR	95% CI	P value	OR	95% CI	P value
N1	1,411	0,815-2,444	0,219	2,601	1,524-4,438	<0,001
N2	1,406	0,768-2,574	0,270	2,508	1,440-4,367	<0,001

OR: Odss Ratio, CI: Confidence Internal

False positive and false negative rates of thorax-CT and PET CT in mediastinal staging of NSCLC were calculated separately for each lymph node (Table 4, Table 5).

False positive and false negative rates were also calculated for N1 and N2 diseases. False positive and false negative rate of thorax-CT in identifying N1 disease were calculated as 53.6% and 28.7% respectively. In the detection of N2 disease, the false positive rate was calculated as 64.6%, while the false negative rate was found as 20%.

Table 4. False positive and false negative rates of thorax-CT in mediastinal staging of NSCLC

LN	2	3	4	5	6	7	8	9	10	11
FP (%)	27,6	-	45,2	40,9	12,5	51,6	0,6	0,4	56,7	0,4
FN (%)	11,1	-	28,9	33,3	80	25	90	100	25	100

LN: lymph node, FP: false positive, FN: false negative

Table 5. False positive and false negative rates of PET-CT (SUVmax 2,5) in mediastinal staging of NSCLC

Lymph Node	2	3	4	5	6	7	8	9	10	11
FP (%)	25	18,8	28,2	26,8	9,4	29,4	1,8	0,0	45,9	0,9
FN (%)	22,2	-	37,8	47,6	70	43,8	80	88,9	27,3	95,9

FP: False positive, FN: False negative

Discussion

Size and localization of masses, lymph node involvement and metastasis are among the factors affecting survival in lung cancer patients as in all oncological diseases [7].

To be able to decide on surgical resection in NSCLC patients, preoperative lymph node involvement must be evaluated, and staging must be done.

Non-invasive and invasive methods are used in evaluating mediastinal lymph nodes. Among the non-invasive staging methods are thorax-CT and PET-CT which are the main radiological scanning methods. Among the invasive diagnosis methods are transbronchial lymph node needle biopsy, endobronchial ultrasound-guided lymph node biopsy, esophageal endoscopic ultrasound guided lymph node biopsy, transthoracic lymph node biopsy, mediastinoscopy, mediastinotomy, VATS, and thoracotomy.

Thorax-CT which is one of the most commonly used non-invasive scanning method in routine cases can be used to find out localization and size of the tumor, its relationship with other anatomic structures (invasion, etc.) and its resectability. While enlarged mediastinal lymph nodes detected in thorax-CT can be shown anatomically, it can not be understood whether these lymph nodes are metastatic or not. In thorax-CT, lymph nodes with a short axis diameter measuring more than 1cm are considered as the limit regarding mediastinal lymph node metastasis. However, due to infection and benign pathologies it is difficult to differentiate enlarged lymph nodes and metastatic lymph nodes. The probability of metastasis in a mediastinal lymph node with a small diameter in thorax-CT is more than 20%. The sensitivity of thorax-CT in mediastinal lymph node staging is 57%, and specificity is around 82% [8].

There is a wide literature on the role of thorax-CT in detecting mediastinal lymph node metastasis. As a result, it was found that thorax-CT is not sufficient on its own to detect metastatic intrathoracic lymph nodes. The results of these studies on the diagnostic performance of thorax-CT are presented here (Table 6).

Table 6. Diagnostic Performance of the thorax-ct in mediastinal staging, Review of literature

Source/Year	Number of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Burry 1997 (9)	64	79	84	58	93
Vansteenkiste/1998 (10)	56	86	79	80	85
Pieterman/2001 (11)	102	75	66	50	85
Dunagan/2001 (12)	72	50	87	56	84
Toloza/2003 (6)	3438	57	82	56	83

According to a study conducted by Dunagan et al]. in 2001 with 72 patients, the sensitivity of thorax-CT in mediastinal lymph node metastasis was found as 50%, specificity as 87%, PPD as 56%, and NPV as 84% [9]. Another study conducted in the same year by Pieterman et al]. calculated sensitivity as 75%, specificity as 66%, PPD as 50% and NPD as 85% [10]. According to the meta-analysis conducted by Toloza et al. in 2003 on the diagnostic performance of non-invasive mediastinal staging methods based on 20 studies with 3438 patients, sensitivity of thorax-CT in detecting mediastinal lymph nodes metastasis was 57%, specificity 82%, PPV 44% and NPV 17% [6] (Table 6). In our study, the sensitivity of thorax-CT in detecting metastatic intrathoracic lymph nodes was found as 75.7%, specificity as 41%, PPV as 27.3%, NPV as 85% and accuracy as 48.4%.

Diagnostic performance of the methods was also evaluated according to the meta-analysis data published by Toloza et al. in 2003 based on a comparison of invasive and non-invasive mediastinal staging methods in NSCLC. In this study, while sensitivity of thorax-CT was calculated as 57%, specificity as 82%, NPV as 83%, PPV as 56% and accuracy as 28%, PET-CT, which is a non-invasive method had 84% sensitivity, 89% specificity, 93% NPV, 79% PPV and 32% accuracy. The sensitivity of transbronchial needle aspiration biopsy, which is an invasive method, was calculated as 76%, specificity as 96%, NPV as 71%, PPV as 100% and accuracy as 70%. On the other hand, the sensitivity of endoscopic ultrasound guided fine needle aspiration biopsy had sensitivity was found as 88%, specificity as 91%, NPV as 77%, PPV as 98% and accuracy as 69%. The sensitivity of mediastinoscopy which is considered as the gold standard in mediastinal staging is 81%, specificity is 100%, NPV is 91%, PPV is 100% and accuracy is 37% (Table 7) [6].

Table 7. Diagnostic performance of the mediastinal staging methods

Methods	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Thorax-CT	57	82	83	56	28
PET-CT	84	89	93	79	32
TBNA	76	96	71	100	70
EUS-NA	88	91	77	98	69
Mediastinoscopy	81	100	91	100	37

However, despite the high diagnostic performance rates for invasive staging methods, due to disadvantages including mortality and morbidity rates, albeit low, and limited sampling of lymph nodes, less invasive or non-invasive methods need to be used.

Patients with NSCLC who have longest survival rates and successful treatment rates are the ones who had an early diagnosis and underwent surgical resection. Therefore, the main feature that is crucial in both non-invasive and invasive methods used for preoperative mediastinal staging is the staging of N factor with the most accurate results.

There are ongoing studies across the world to find the fastest, most accurate, and least invasive method by making a comparative analysis of different mediastinal staging methods. Our study aims to demonstrate the role of thorax-CT, which has become the standard scanning method, in mediastinal lymphatic staging. We aim to determine whether non-invasive methods could serve as an alternative to invasive methods in mediastinal lymphatic staging.

Thorax-CT plays a central role in the diagnosis and staging of lung cancer. It gives useful information with regards to the localization of the tumor in the thorax, its size, resectability, its relationship with anatomic structures (T state) and detection of metastatic mediastinal lymph nodes (N2 state). Lymph nodes measuring more than 1cm in the short axis diameter are considered as suspicious regarding metastasis. However, while the

rate of detection of metastasis in non-pathological small lymph nodes could be 15-20%, in enlarged lymph nodes, the rate for detection of non-metastasis could be 40% [11, 12].

In our study, sensitivity of thorax-CT in detecting intrathoracic lymph nodes is 75,7%, specificity is 41%, PPV is 27,3%, NPV is 85% and accuracy is 48,4%. False positive and negative rates were identified or N1 and N2 diseases. False negative rate and false positive rate of thorax-CT in identifying N1 disease were calculated as 53.6%, and 28.7% respectively. False positive and false negative rate for identifying N2 disease were found as 64.6% and 20% respectively.

Our study found that specificity of thorax-CT and PPV were lower than other studies (Table 6). While this is statistically meaningful, we believe that it is due to the bigger size lymph nodes caused by infectious and granulomas diseases, which are common in Turkey.

Following the statistical analysis, it was found that thorax-CT on its own is not an effective scanning method in detection of metastatic intrathoracic lymph nodes however it is still an important method regarding identifying the anatomic localization of the mass, its resectability and its relation to surrounding tissues. While thorax-CT could be performed before the additional invasive methods in mediastinal staging of the lymph nodes, its use together with the non-invasive methods would also make a positive impact on the diagnostic performance indicators.

This study aims to review our knowledge on thorax-CT which is the most commonly used scanning method in lung mass and to discuss its role in mediastinal staging based on the data derived from patients in Turkey.

Although thorax-CT is an indispensable scanning method for mediastinal staging in NSCLC, it must be noted that its sole use is not sufficient and it should be supplemented with other scanning techniques and invasive methods. Following our study which aimed to refresh our knowledge, we would like to emphasize that considering the increasing health costs and the waste of time and labor due to the use of more than one scanning method, the combination of PET and CT must be resorted more. As the data on the use of PET and MR combination in several health centers in recent periods become available, we believe that there might be different developments about the use of non-invasive methods in mediastinal staging.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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